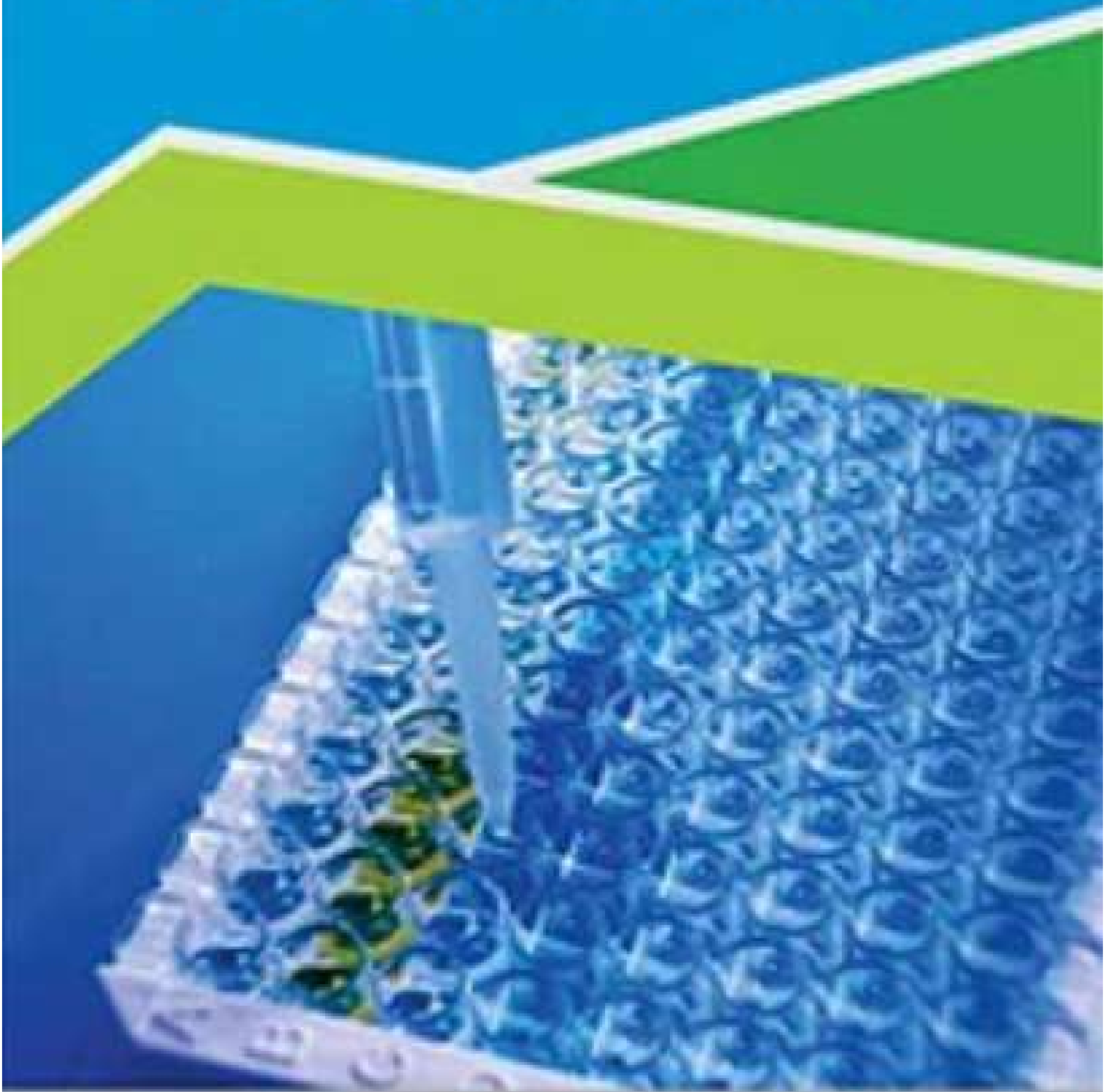


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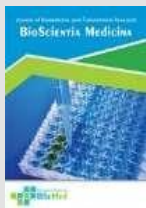
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The Effectiveness of Combination Therapy of Needling and Secretome from Mesenchymal Stem Cells (Serum 10%) for Acne Scar Treatment

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ABSTRACT

Background: Acne scars can have various impacts on individuals, both physical and psychological. Acne scars arise as a result of complications from acne vulgaris. This study purposed to determine the effectiveness of the treatment using a combination of SC-PWJMSC with microneedling for acne scars. **Methods:** Pre-post clinical trial involving patients with acne scar. The intervention used in this study was a combination therapy of microneedling and secretome from mesenchymal stem cells. The intervention was carried out 1 time and monitored for 42 days. Primary outcome in the form of Observer visual scar assessment scale (OVSAS) was assessed at baseline and 42nd day, Secondary outcome (regenerative parameters) was assessed at baseline, 21st day and 42nd day. **Results:** There was a significant change in the primary and secondary outcomes (p-value <0.001) without any significant side effects. **Conclusion:** This study showed that combining needling with secretome from mesenchymal stem cells (MSCs) led to satisfactory results in repairing acne scars and in a number of other ways (secondary outcomes). On the other hand, there are limitations in this study in the form of no comparison therapy for the treatment of acne scar.

1. Introduction

Acne vulgaris (AV), or what is known as acne, is a skin disease that often occurs and can heal by itself. Even though it can heal on its own, it is always a problem in society, especially during adolescents and young adults. Acne itself often causes acne scars in the form of scars, which can cause psychological burdens, such as stress, embarrassment, and inferiority.¹

The aetiology of acne vulgaris is multifactorial, including genetics, race, hormonal, stress, cosmetics, diet, drugs, etc. Acne vulgaris has a prevalence above 90% in the adolescent population and persists into adulthood in 12-14% of cases. There are 4 most

influential pathologies that can cause acne, namely increased sebum production, hyperproliferation of pilosebaceous follicles, colonization of *Cutibacterium acnes* (*C. acnes*), and inflammatory processes.^{1,2} A possible complication of acne vulgaris is acne scars which, although they can be treated in various ways, can have a negative psychological impact. The prevalence of acne scars affects approximately 95% of patients and is related to the severity and delay of treatment.^{3,4}

The most common types of acne scars are atrophic and hypertrophic types. The pathogenesis of acne scars is still not fully understood, but several hypotheses have been proposed.² Currently there are

many treatments for acne scars, some of which are dermabrasion, dermaroller/needling and combination therapy. Dermabrasion works by mechanically removing layers of damaged skin to increase re-epithelialization. Meanwhile, dermaroller/needling is done by making thousands of micro punctures on the skin to induce the production of growth factors and collagen.^{3,5} Various modalities have been used to treat acne scars, but limited effectiveness and side effects limit their application.⁶

Mesenchymal stem cells (MSC) have an effect on cell regeneration and tissue repair. MSC has been scientifically proven to reduce atrophic and hypertrophic acne scars.⁶ The secretome of MSC contains many growth factors, chemokines, and cytokines which work as pro-angiogenic factors and trigger endothelial, epidermal, keratinocyte and fibroblast migration and proliferation for re-epithelialization of acne scars.^{7,8} The combination of MSC treatment with dermabrasion and dermaroller is thought to provide optimal results for reducing acne scars with minimal side effects and complications, and faster healing time.^{6,9}

Since there are no study about the combination treatment of MSC and dermabrasion/dermaroller among acne scar patients in Indonesia, we sought to investigate the effectiveness of the treatment using a combination of secretome of placental Wharton jelly mesenchymal stem cell (SC-PWJMSC) with microneedling for acne scars in Indonesia.

2. Methods

Study design

This is a single-center study with a pre-post clinical trial (quasi experimental). The study was approved by Universitas Tarumanagara Human Research Ethics Committee Institution of Research and Community Engagement.

The subjects of the study

Patients with atrophic acne scars who met the inclusion criteria and were treated at Sukma Cliniq Tangerang, were included in this study. The inclusion

criteria were age of 18 to 70 years, good health, Global Acne Scarring Classification grades 2 through 4, and at least two regions of acne scarring on the face (with at least three distinct acne scars in each area). The exclusion criteria included history of keloids or hypertrophic scars, skin infection or active skin disease other than mild acne in or around the study areas, active systemic or local skin disease likely to alter wound healing, treatment with injectable fillers or ablative or nonablative laser resurfacing to the study areas within the previous 6 months or pending treatment with isotretinoin or other oral retinoids within the next 6 months, and medication with isotretinoin or other oral retinoid.

Research procedure

Each participant's medical history was documented at the screening and baseline visit. The digital images at baseline, i.e., anterior and 45° lateral view in a bespoke device that stabilizes the chin and forehead were obtained using a Skin Analyzer. Participants were instructed to stop using any topical peeling drugs or topical vitamin A treatments on their faces one week before treatment and to continue doing so for at least four weeks following their final treatment. The treatments included microneedling therapy, secretome delivery, and evaluation of primary, secondary, and tertiary results. Before each treatment, digital photographs and adverse events (such as infection, prolonged erythema, prolonged oedema, serosanguineous drainage, bleeding, ulceration, erosion, and pigmentation) were taken, as well as their duration, resolution, intensity, relationship to the study procedure, and any curative actions taken.

Needling procedure

A topical anesthetic (Lidocaine 2.5%, Prilocaine 2.5%) was administered to the treatment area for 1 hour under occlusion before each visit. Following the removal of the topical anesthetic, the skin was cleansed with chlorhexidine and the appropriate treatment was delivered. Clinical examination of skin

thickness and scar severity was used to determine the roller depth. A 1.0-mm device was utilized if scars looked to be exceptionally fine and the person had less sebaceous, fine skin, as was the case in some female participants; otherwise, a 2.0-mm device was employed. During each procedure, the device was rolled over the skin in each of eight linear directions around the midpoint of the study treatment area (e.g., north to south and back, northeast to southwest, east to west, southeast to northwest, and so on), traversing the treatment area a total of 16 times end to end. Following the procedure, the pain level was measured using a 10-point visual analogue scale. Gentle manual pressure with gauze was provided for 5 minutes immediately following each treatment to control pinpoint bleeding and serum secretion. The skin was bathed for an hour with saline swabs to aid hydration, while the individuals were instructed on the importance of home care.¹⁰

Secretome profile

A 5% secretome (SM) serum was administered throughout the needling action to heal acne scars. In this study, the intervention was secretome of human umbilical cord mesenchymal stem cells (SM-hUCMSC). Mesenchymal stem cells obtained from the umbilical cord were grown in a T175 Flask (Corning) until passage 6 (P6). After reaching 70-80% confluence, the culture media was deprived and replaced with baseline medium with no supplement addition, and the cells were incubated at 37°C under hypoxic condition (5% CO₂ incubator). The conditioned media was collected after 72 hours of incubation and stored in a deep freezer (-80°C) for long-term storage. 10% serum was added to the SM-hUCMSC.

We used passage six cells for CM synthesis due to their specific MSC properties. MSC cells were grown in MEM-Alpha without a growth supplement at 70-80% confluence. The MSC cells were cultured for a further 72 hours to allow the secretome to be secreted. To establish the best conditions for secretome secretion, MSCs were subjected to hypoxic [5% O₂] settings. To

preserve the protein content of the CM for long-term preservation, it was placed in a deep freezer. We analyzed the protein contents of the CM (by ELISA), which showed the pro-collagen 1 level was 655,100.00 pg./mL, vascular endothelial growth factor (VEGF) level was 21.42 pg./mL, and basic fibroblast growth factor (bFGF) level was 34.64 pg./mL.

As much as 1 ml of Wharton Jelly Mesenchymal Stem Cells Conditioned Medium/ WJM-SC-CM (100%) containing VEGF, bFGF, ProCollagen, Keratinocyte Growth Factor (KGF), and numerous growth factors, paracrine, and cytokines was mixed with 9 grams of serum mixture to make 10% serum. Periodic product stability testing has been performed to assure the stability of the growth factor content. Sterility, microbial, and endotoxin testing on gel formulations were also performed in accordance with Good Laboratory Practice (GLP) standards.

Intervention

Every patient who met the inclusion requirements was given an explanation by the doctor regarding the intervention's procedures. The intervention in this study was the needling with a mixture of 10% secretome serum to repair acne scars (at the time of intervention and home use for 21 days). The intervention will be carried out on day 0 according to the procedure previously described and measured repeatedly on day 21 and day 42. In each measurement, primary, secondary, and tertiary research variables will be assessed.

Outcomes

The primary outcome measure was the OVSAS. This system assesses scar appearance by counting vascularization, pigmentation, and thickness (0-10 for each item), with higher scores indicating more scarring.¹¹

In addition to healing acne scars and side effects, this study also describes the effects of action on anti-aging and tissue regeneration parameters as the secondary outcomes. The related parameters are RGB Pore, RGB Spot, RGB Wrinkle, RGB Roughness, UV

Porphyrin, UV Pigmentation, UV Moisture, UV Damage. All these parameters were assessed using a Skin Analyzer. The result of this parameter is the average measurement of the 3 facial areas according to the T Zone and V Zone.¹²

3. Results

The study included 21 respondents who met the inclusion criteria. The basic characteristics of respondents are presented in Table 1. The intervention lasted for 42 days with measurements of primary and secondary variables on day 0 (before intervention), day 21 and day 42.

Table 1. Basic characteristics of respondents.

Parameter	N (%)	Mean (SD)
Age		38,67 (12,46)
Gender		
Male	8 (38,1%)	
Female	13 (61,9%)	

All changes and improvements in the variables are presented in Table 2. All parameters in secondary outcomes showed significant improvement. For example, Figure 1 shows improvement of the UV damage parameter from day 0 (left), day 21 (middle),

and day 42 (right) of using secretome. Monitoring of side effects was conducted periodically for up to 3 months post-intervention and no significant side effects were found for 3 months post-intervention.

Table 2. Primary and secondary outcomes of the study.

Parameter	Average observation value, mean (SD)			p-value
	Before intervention (Days-0)	After intervention (Days+21)	After intervention (Days+42)	
Primary outcome*				
Observer visual scar assessment scale (OVSAS)	16,48 (2,54)	N/A	10,95 (1,72)	< 0.001
Secondary outcomes**				
Pore	18,81 (4,39)	23,33 (6,94)	27,19 (8,18)	< 0.001
Spot	14,38 (2,84)	17,57 (7,63)	21,29 (11,57)	< 0.001
Wrinkle	22,24 (8,10)	27,86 (14,33)	32,24 (17,16)	< 0.001
Roughness	20,24 (6,11)	25,29 (9,75)	29,33 (11,87)	< 0.001
UV porphyrin	59,19 (14,10)	64,71 (12,98)	67,9 (12,99)	< 0.001
UV pigmentation	52,29 (15,39)	55,76 (16,51)	60,10 (15,64)	< 0.001
UV moist	56,57 (11,52)	59,95 (11,26)	62,29 (11,62)	< 0.001
UV damage	31,52 (10,54)	34,67 (11,69)	38,81 (13,13)	< 0.001
N/A: Not Applicable; UV: Ultraviolet; *Statistics test using Paired T-Test; **Test statistics using Repeated Measurement.				

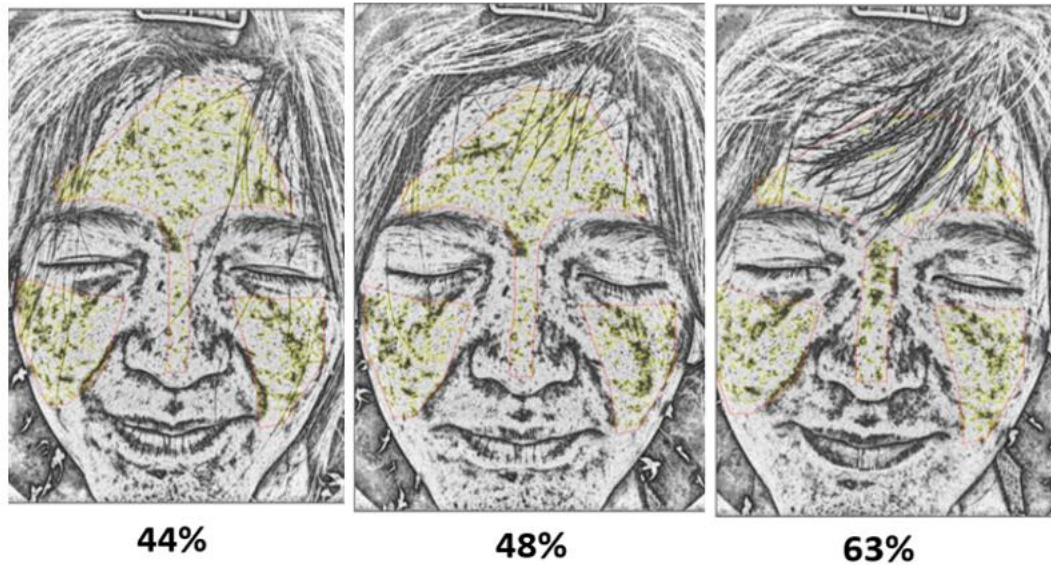


Figure 1. UV damage repair during 42 days of using secretome; Baseline (Left), Day 21 (Middle), and Day 42 (Right).

4. Discussion

Hypertrophic acne scars and keloids are associated with excess collagen deposition and decreased collagenase activity. Hypertrophic scars are usually pink, raised, and firm, with thick hyaline collagen bundles that remain within the boundaries of the original wound site. The histology of hypertrophic scars is similar to that of other skin scars. In contrast, keloids present as reddish-purple papules and nodules that proliferate beyond the boundaries of the original wound. Histologically, they are characterized by thick hyaline acellular collagen bundles arranged in whorls. Hypertrophic and keloid scars are more common in darker skinned individuals and occur mainly on the trunk.¹³⁻¹⁵

Needling is a recently proposed technique that involves using a sterile roller consisting of a series of sharp and fine needles to puncture the skin. Needling is useful for inducing collagen. First, the facial skin must be disinfected, then a topical anesthetic is applied, and left for 60 minutes. The skin needling procedure is achieved by rolling the tool on the area of the skin affected by acne scars, back and forth with some pressure in different directions. The needle penetrates about 1.5 to 2 mm into the dermis. With this technique, rolling is usually continued until bruising occurs, which induces a growth factor

complex that ultimately results in collagen production. Results generally start to be seen after about six weeks, but full effects can be seen in as little as three months and, because collagen deposition occurs slowly, skin texture will continue to improve over a 12-month period. Acne scars that are suitable for dermarolling are rolling scars and superficial boxcar scars. Compared to other procedures, this technique has many advantages. First, it is safe on all skin types and has the lowest risk of post-inflammatory hyperpigmentation when compared to laser, chemical peels, or dermabrasion procedures. Second, the treatment does not produce a line between treated and untreated skin. Third, the recovery period is significantly shorter than for other procedures. Dermaroller also costs less than lasers and other procedures.^{3,13}

Secretomes from mesenchymal stem cells (MSCs) have become an interesting area of research in skin regeneration. MSC is a type of stem cell that has the ability to differentiate into various types of cells in the body, including skin cells. The secretome of MSC contains various growth factors, cytokines, proteins and other bioactive molecules which have a positive effect on skin regeneration and healing. MSC secretome contains growth factors and other bioactive molecules that can stimulate the regeneration and

healing of skin tissue damaged by acne scars. Growth factors such as epidermal growth factor (EGF) and transforming growth factor-beta (TGF- β) can stimulate the proliferation of new skin cells and the synthesis of extracellular matrix, helping to repair damaged tissue and reduce the appearance of scars or pimple. In addition, the MSC secretome contains anti-inflammatory cytokines such as interleukin-10 (IL-10) and hepatocyte growth factor (HGF) which can reduce inflammation in the skin. These helps reduce the inflammatory changes associated with acne scars and promotes better healing. All of the above processes will lead to extracellular matrix remodelling: Acne scars are often caused by changes in the extracellular matrix, including an increase in irregular collagen production.^{16,17} MSC secretomes can affect the synthesis and degradation of the extracellular matrix through components such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). By adjusting this balance, the secretome can help reduce the appearance of acne scars and improve the quality of newly formed skin.^{16,18}

In our previous study, we also have shown the effectiveness of 10% SM-hUCMSC in accelerating the process of chronic wound (diabetic and tropical ulcer) healing without any reported side effects. It also has been known that MSC-CM has anti-inflammatory properties and several factors in modulating also inducing skin regeneration and decreasing post-inflammatory fibrosis. Collagen and elastin production by fibroblast also increased, thereby increasing wound healing rate.¹⁹

5. Conclusion

This study revealed that the use of combination therapy in the form of needling with secretome from mesenchymal stem cells (MSCs) gave satisfactory results in acne scar repair and various other regenerative parameters (secondary outcome). On the other hand, this study still has limitations, namely the absence of comparisons with other intervention groups. Therefore, in future studies it is hoped that a

randomized controlled trial (RCT) will be carried out by comparing single therapy in the form of needling (negative control); needling combination therapy with secretome; and needling combination therapy with vitamin C (positive control).

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